PATENT
Attorney Docket No.8076.102USF2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
HADDADA et al)
) Group Art Unit: 1632
Serial No.:08/619,157)
) Examiner: S. Priebe
Filed: March 21, 1996)

For: DEFECTIVE RECOMBINANT ADENOVIRUSES EXPRESSING CYTOKINES FOR USE IN ANTITUMORAL TREATMENT

DECLARATION PURSUANT TO 37 C.F.R. §1.132

I, Majid Mehtali, do hereby declare and state the following:

1.) That I have received an Engineer Diploma in Biotechnology in 1985 from the European School of Biotechnology of the Upper Rhine Region, Strasbourg, France. In 1988, I received a Ph.D. in Molecular Biology at the Institute of Molecular Genetics at the University of Strasbourg in France.

2.) In 1984 I worked for three months at Roche in the laboratory of Dr. R. Thon and in 1985 I worked nine months at Rhone-Merieux in Lyon, France in the laboratory of Dr. G. Chappuis. I have been employed at Transgene S.A. since 1988 and I currently head the Gene Therapy Department at Transgene S.A. Enclosed, please find a copy of my *Curriculum vitae*.

3.) I have read and understood the above-captioned patent application, as well as the pending claims of record. I have also read and understood the latest Official Action issued by the U.S. Patent and Trademark Office on February 3, 1998.

It is my understanding that Claims 1 and 3 to 8 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Rosenfeld et al taken with Russell, Ramshaw et al and Stratford-Perricaudet et al. It is my understanding that this rejection means that the claims of record were obvious to the skilled scientist when their teachings are combined.

4.) I have reviewed the publications of Rosenfeld et al, Russell, Ramshaw et al and Stratford-Perricaudet et al that were cited in the above-mentioned Official Action. It is my opinion that a skilled scientist would not come to the same conclusions as the Examiner has for the following reasons.

5.) First of all, as I understand, the present invention relates to a defective adenoviral vector and an insert containing a nucleic acid sequence coding for a cytokine. The defective adenoviral vector lacks the transactivators E1A, E1B and the E3 region of the adenovirus. The defective adenoviral vector can be used to treat tumors. Although it was known prior to the filing of this application that cytokines have been used to treat tumors with some success via systemic injection, side effects such as fever, fluid retention and life-threatening vascular leak syndrome often resulted due to the high dosage given to the patient which was needed to treat the tumors. To solve this problem use of a different type of delivery system was necessary for making the tumor cell a source of cytokine production without severe toxicity.

6.) Prior to the filing date of the present application, which I understand is March 18, 1992, many vector systems were available for use to the skilled scientist. The different vector systems available then included vaccinia virus, pox virus, HTLV-I, retroviral vectors, herpes virus, bacterial vectors, human parovirus vectors such as human AAV and H1, as well as the mouse vector MVM p, synthetic vectors and adenoviral vectors. However, to the best of my knowledge there was no precise guidance given to the skilled scientists to make a particular selection among the known vectors to treat cancerous tumors. In fact, among the various known vectors there were often problems associated with th ir use. This, was for example, reviewed in the Russell reference, which is discussed below.

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7.) It is my opinion that from th teachings of Russell, a skilled scientist would glean that this reference teaches against using a defective recombinant vector due to the problems associated with access by defective vectors to poorly vascularized tumor regions. This is clear from the teachings at page 198, first column.

Moreover, Russell recognizes the need to develop suitable vectors for gene delivery and expression, since in 1990 there were problems associated with the vector systems. However, there is no teaching in Russell concerning what vector systems would in fact work. The only guidance given to the skilled scientist in Russell was the recognition that competent viral vectors should be chosen since they could facilitate infection of a higher proportion of tumor cells.

8.) Ramshaw et al disclose a variety of vaccine vector systems such as poxvirus, ~~vaccinia virus~~, herpes virus, adenovirus or bacteria in which a nucleic acid encoding a lymphokine is disclosed. The vaccine vector systems described in this reference are competent and thus viable vectors. The reason why Ramshaw et al teach the use of viable vectors is to enhance the immune response to the antigenic polypeptide that is expressed, which can be a "native" sequence of the host vector itself. Therefore, the skilled scientist would not use defective vectors to accomplish the teachings of Ramshaw et al.

Moreover, the Examples clearly demonstrate that vaccinia virus was the vector of choice. Although Example 4 illustrates a competent adenoviral vector only lacking the E3 region it appears that this example is a mere afterthought.

9.) It is my understanding that the Examiner has relied on the teachings of Rosenfeld et al to encourage the use of adenoviral vectors in which the entire E1 region can be removed. More specifically, the Examiner deems that following teaching in Rosenfeld would encourage a skilled scientist to delete the E1 region:

> Most human adults have antibodies to one of the three serogroup C adenoviruses to which Ad5 belongs (5). This implies little risk to those

working with these vectors but may have negative implications for the virus as a gene transfer vector in the human lung. If such problems are encountered alt ration in the vector construct may be helpful.

However, this paragraph cannot be interpreted as meaning that the E1 region should be deleted. Indeed, this paragraph means that most human adults have antibodies to adenoviruses and hence repeated administration of the adenoviral vector may result in the antibodies "killing" the administered adenovirus and therapy would not be effective. If this is the case, one would have to alter the vector such that the antibodies would not recognize the surface of the virus or the capsid. It should be noted that the E1 region is not within the capsid.

Moreover, the entire E1B region in the construct of Rosenfeld et al is maintained, as well as the 3' part of the E1A coding region from 936 to 1540 bp.

Thus, it is my opinion that a skilled scientist would not be guided to remove the E1A and E1B regions from the teachings of Rosenfeld et al. Moreover, this reference relates to defective gene therapy and not to threat tumors which is discussed more extensively under point 11 below.

10.) Stratford-Perricaudet et al teach the use of defective adenoviral vectors for selective delivery to certain tissues. It is clear to the skilled scientist that this publication is a general overview of the promising aspects of using adenoviral vector constructs for use in certain gene therapies such as OTC and other enzyme deficiencies directed to therapy of genetic diseases, which restores a defective function *in vivo*.

A skilled scientist would not know from reading this reference if an adenoviral vector can be used to treat cancerous tumors, since Stratford-Perricaudet et al teach replacement gene therapy.

11.) Cancer th rapy is totally different from therapy that restores a defective gene. For example, recombinant cytokines were known to have a very short half-life

in vivo resulting in the necessity for continuous infusions or regular injections. The same is not true for many replacement therapies.

Secondly, local delivery of cytokines, and especially IL-2 had added difficulties of access to tumor deposits and is totally inadequate for occult metastic disease. This is a different situation from replacement gene therapies where certain tissues such as the lung lacking α-1AT, for example, could be targeted.

Thirdly, adenoviral vectors were known to be quite immunogenic; i.e., Rosenfeld et al recognized this problem. Although this immunogenicity may be a disadvantage for some gene therapies, it is beneficial for immunotherapy since this immunogenicity will limit the duration of cytokine expression and provide adjacent stimulous for the development of antitumor immunity.

In conclusion, it is my opinion that gene therapy to threat tumors is different from gene therapy to correct a deficient gene. Thus, a skilled scientist would not necessary interchange a "delivery system" for gene therapy of genetic diseases and cancer therapy without some suggestion or guidance given in the scientific literature that it is feasible.

12). I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Nov. 18, 1998
Date

Majid Mehtali, Ph.D.

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Submitted.

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CURRICULUM VITAE

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PERSONNAL

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EDUCATION :

High School, Saint-Louis, France
1980 : Baccalaureat D (Mathematics, Physics, Biology)

European School of Biotechnology of the Upper rhine Region, Strasbourg, France
1982-1985 : Engineer Diploma in Biotechnology

University of Strasbourg, France
1980-1982: Diploma of General Biological University Studies (DEUG. B)
1983: Licence in Biochemistry
1984: Maitrise in Biochemistry
1985: D.E.A. in Molecular Biology (equivalent to Msc)
1985-1988: PhD in Molecular Biology at the Institute of Molecular Genetics (Director: Pr. P. Chambon). Topic: *in vitro* and *in vivo* (in transgenic mice) analysis of the role of specific regulatory sequences from housekeeping genes

PROFESSIONAL EXPERIENCE :

1984: 3 months period at Roche (Basel) in the laboratory of Dr. R. Then (Pharmaceutical Research Dpt); topic: biochemical analysis of the bacterial porins isolated from antibiotic-resistent strains.

1985: 9 months period at Rhône-Mérieux Company (Lyon, France) in the laboratory of

Dr. G. Chappuis; topic: identification and biochemical characterization of the pathogenic agents (later shown to belong to the Pestiviruses virus family) responsible for bovine and porcine diseases.

1988: Staff Scientist at Transgene S.A.
Research projects:
(i) development of novel transgenic animal models (mice and rabbits) for the evaluatation of potential anti-HIV1 treatments and characterisation of the role of major HIV regulatory proteins in AIDS pathogenesis;
(ii) producion and evaluation in rhesus and cynomolgus macaques of various recombinant AIDS vaccine candidates (Live attenuated viruses, recombinant purified viral proteins, poxvirus-derived vaccines, pseudovirions,...).

1991-1992: Head of the Virology-Immunology department at Transgene S.A.
Research projects:
(i) development and evaluation of candidate AIDS vaccines;
(ii) development and evaluation of new immunotherapeutic approaches for breast cancer.

1992-1998: Head of the Gene Therapy department at Transgene S.A.
Research projects:
(i) development of novel generations of safer and more efficient viral (human and animal adenovirus, murine retrovirus, simian lentivirus) and cellular vectors for gene therapy;
(ii) development and evaluation *in vitro* and *in vivo* of gene therapy strategies for cancer, AIDS, Heamophilia and cardiovascular diseases;

For Utility, PCT, and Design Applications

MERCHANT & GOULD

United States Patent Application

▼ INSTRUCTIONS

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert TITLE of invention: DEFECTIVE RECOMBINANT ADENOVIRUSES EXPRESSING CYTOKINES FOR ANTITUMOR TREATMENT

Check a or b

The specification of which

a. ☒ is attached hereto

b. ☐ was filed on November 10, 1993

If "b" checked, complete

as application serial no. 08/150011

and was amended on _____ (if applicable)

If PCT Application

(in the case of PCT-filed application)

Insert Int. application number & filing date

described and claimed in international no. PCT/FR 93/00264 filed March 16, 1993

and as amended on _____ (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a). (Reprinted on back side).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent of inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

Prior applications
Check a or b

a. ☐ no such applications have been filed.

b. ☒ such applications have been filed as follows:

If "b" checked, complete

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC §119			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
FRANCE	9203120	16/03/1992	
ALL FOREIGN APPLICATIONS, IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

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I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

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SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE: DEC. 15, 1993	DATE: DEC. 15, 1993	DATE: DEC. 15, 1993

Each inventor must sign & date

Note: No legalization or other witness required

For Additional Inventors:

☐ Check box and attach sheet with same information, including date and signature.

Revised 11/1/92